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HARRIET M. STRIMPEL, D. Phil.
New England Biolabs, Inc.
240 COUNTY ROAD
IPSWICH, MA 01938-2723

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STRIMPEL@NEB.COM
Goldberg@neb.com
wermuth@neb.com

RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GEORGE TZERTZINIS, GEORGE FEEHERY,
CORINNA TUCKEY, CHRISTOPHER NOREN,
and LARRY McREYNOLDS

Appeal No. 2009-004205
Application No. 10/622,240
Technology Center 3600

Oral Hearing Held: November 5, 2009

Before DEMETRA J. MILLS, LORA M. GREEN, and FRANCISCO C. PRATS, *Administrative Patent Judges.*

APPEARANCES:

ON BEHALF OF THE APPELLANTS:

DR. HARRIET STRIMPEL, ATTORNEY
New England Biolabs, Inc.
240 County Road
Ipswich, Massachusetts 01938-2723

The above-entitled matter came on for hearing on Thursday, November 5, 2009, commencing at 9:45a.m., at the U.S. Patent and

Trademark Office, 600 Dulany Street, Alexandria, Virginia, before Paula Lowery, Notary Public.

P R O C E E D I N G S

THE CLERK: Good morning. Calendar Number 35, Ms. Strimpel.

JUDGE MILLS: Good morning. I don't know if you've been with us before, but you have 20 minutes that you can use however you'd like. However, it would be very helpful to us if you would focus on what you believe are the most important issues in the case.

If you wouldn't mind introducing who you have with you this morning.

DR. STRIMPEL: I'm here today with Dr. George Tzertzinis, who is the first-named inventor on the application at issue.

I am Dr. Harriet Strimpel. I'm Chief Patent Counsel at New England Biolabs.

I just want to mention New England Biolabs is a 35 year old biotechnology company that provides high quality products to the scientific research community. We count a Nobel Prize winner among our scientific staff.

The claimed method and composition before you is no exception to the quality of work that we try to do, and that's manifested by the fact that Bishop's Lab has produced an additional paper and have used our method, despite the fact that Yang actually is a member and comes from Bishop's Lab. The claimed invention has been allowed in Europe and Japan.

So now I'm going to stick to the task of talking to you about within the confines of the Brief that you have read why our claimed invention is not obvious over the cited art.

I want to address, in particular, Claims 1 and 13, which are the composition claims. Claim 1 is an independent method claim. Actually, there's an additional independent method claim, Claim 12, but it relies in entirety upon the method claim in Claim 1. Claim 13 is a compositional claim.

The salient point I want to mention is the technical problem that was addressed by the claims. The technical problem was to produce fragments of 15 to 30 nucleotides that were represented of a large double-stranded RNA by enzymatic digestion.

The problem was that our RNA string was not meeting in the buffer cuts double-stranded RNA to fragments of 12 to 15 nucleotides. That was the conventional art.

We have developed an improvement, which we have claimed, which requires a transition metal ion in the buffer, and that results in the consistent production of fragments of 15 to 30 nucleotides.

The Claim 1 salient points are that we desire to produce fragments of 15 to 30 nucleotides. We start with large double-stranded RNA with RNA string. We utilize transition metal cut irons, and we use an enzyme to a substrate ratio of greater or equal to .25 to 1.

The composition claim that I will also address is a set of 15 to 30 nucleotide fragments where a substantial portion of the sequence of one or

more large double-stranded RNA is represented in the fragments of 15 to 30 nucleotides.

UDGE MILLS: Have you defined what you mean by substantial portion?

DR. STRIMPEL: Yes, we've defined it in the application and the definition section, Paragraph 0088, where a substantial portion refers to the amount of the sequence that is represented by greater than 20 percent of the entire large double-stranded RNA.

JUDGE MILLS: I don't know if you could directly address the question of whether the divalent metal of Gross is not readily substitutable for the magnesium of Yang.

DR. STRIMPEL: Well, in the first case, I want to say that magnesium -- just to point out -- is an alkaline metal, whereas manganese is a transition metal.

In my comparison of the two references, in particular I'd like to say Gross is trying to do something quite different from Yang. The important thing is Yang is actually a relevant reference in the sense that they were tackling the same problem we were, which was to solve the problem that RNaseIII is an enzyme potentially for generating fragments of 15 to 30 nucleotides had this problem of exhaustive digestion, which resulted in fragments of 12 to 15 base pairs.

Yang solved that problem by changing -- playing with the amounts of the enzyme and the time of incubation so as to get the desired fragment size. Gross doesn't address -- it's a totally different thing. It's looking at viral RNA, which is single-stranded, which happens to fold into a hair pin so that

the regions of the viral RNA are double-stranded. But the double-stranded regions at no time are greater than 12 nucleotides in length.

So the problem of reducing the cleavage so that instead of getting 12 to 15 nucleotides you get 15 to 30 nucleotides is a problem that is never presented in Gross. It's never an issue.

In fact, Yang has a Gross reference. It's a 1987 reference. The Yang Laboratory in San Francisco, which has Bishop as a named inventor on that patent application, he also had a Nobel Prize. He would have known full well about Gross and other references in which the impact of manganese on specific cleavage of viral single-strand RNA was published.

In fact, they didn't choose to use that because it seemed the better route for them to look at amounts and times. It's because our company focuses on enzymes in general it was suggested and followed up, why not try manganese? Even though whatever was known about use of manganese was expected to have a contrary effect.

It was surprising when manganese was used that it had this particular effect in this method to generate a stable band which was a big improvement over Yang because it didn't require an additional proliferation to get the size that you desired.

JUDGE MILLS: With respect to the product claim, which doesn't include the manganese limitations or the ratio, could you address why it wouldn't have been obvious to one of ordinary skill in the art to adjust the amount of enzyme or the time, as you indicated it teaches, and come up with a 15 to 30 nucleotide product?

DR. STRIMPEL: You would have to assume you would have completely random cleavage in order to have a representation, even if it was inefficient of enzyme digestion. So RNase -- you would have to assume that that was the case. So the fact the enzyme was either overly efficient or underly efficient would be compensated for in a lot of starting material.

But if there's a bias, if you did not know that fact that it was random, but assumed there was a bias, which is indicated by Gross, where you've got specific cleavage sites that manganese seems to suggest. It seems to cleave at specific cleavage sites in that RNA.

You would expect that to be a bias in the fact that there would be some regions of the RNA that the larger, double-stranded RNA would be cleaved. Either better than others, or totally that some areas of the large double-stranded RNA would not be cleaved at all.

In which case you would not have a representative fraction -- substantial portion of the large double-stranded RNA represented.

JUDGE PRATS: Excuse me, if I may, doesn't Yang -- I'm looking at Paragraph 53. It's a long paragraph, but about half-way down the page: "RA3 has a lack of sequence specificity in substrate recognition."

DR. STRIMPEL: It does say that.

UDGE PRATS: If I may, doesn't that mean that at least in Yang's hands when Yang did his digestion, you actually would expect a lot of overlap?

DR. STRIMPEL: You would expect that. The only problem -- that's absolutely incorrect. Thank you for pointing that out.

In fact, if you look at what Yang achieved because they had to be very precise about the time and the amount of enzyme they used, it resulted in what you see in Figure 1B of the Yang reference, which we have a larger blow-up of.

It's actually rather difficult to decipher, and we can show that to you. What you see is a large blob, a smear, in which you've got large fragments and small fragments, and they cut out a band which corresponds to the marker, which is a 21 nucleotide band.

If the enzyme favored certain sequences and they were not correct because they didn't demonstrate that they had this completely random cleavage, then they would lose a chunk of their double-stranded RNA after cleavage to small fragments, and some of it would be uncleaved.

So the selected band that actually cleaved correctly at the 21 nucleotide band would not be representative -- would not be a substantial portion of the double-stranded RNA.

In other words, what I'm trying to say is because with manganese, instead of magnesium which appears to have a different effect and different mechanism with respect to the RNA.

JUDGE PRATS: Right. Let me be a little more direct. Why isn't Claim 13 anticipated by Yang?

DR. STRIMPEL: Because Yang doesn't demonstrate it. They have no idea -- that is simply --

JUDGE PRATS: Yang is the same enzyme, the same substrate. We just established that they, in fact, create an overlapping population of

molecules, and they have the same size. They say they want to do 20 to 25, which limitation is missing from Claim 13 in what Yang discloses.

DR. STRIMPEL: Because they're using magnesium.

JUDGE MILLS: Claim 13 --

JUDGE PRATS: The claim requires a certain set of molecules, which I'm confused why that isn't disclosed by Yang.

DR. STRIMPEL: Because of the fact that the nature of the way the RNase really digests double-stranded RNA in the presence of magnesium because it digests very rapidly. So at any one time you have a mixture of fragments. Some are too small, some are too large.

JUDGE PRATS: If I may, Claim 13 only requires some of the fragments to be 15 to 30. Yang discloses they've got their fraction being 20 to 25, don't they?

DR. STRIMPEL: Yes, that's right.

JUDGE PRATS: So that's within your claimed range.

DR. STRIMPEL: But it's because the substantial portion requires that a certain amount of a double-stranded RNA is represented by those fragments.

JUDGE MILLS: Meaning 20 percent?

DR. STRIMPEL: At least 20 percent.

JUDGE MILLS: And you don't get that when you digest with magnesium.

DR. STRIMPEL: That's correct.

JUDGE PRATS: We have evidence of that on the record?

DR. STRIMPEL: That you don't get 20 percent of the -- but there's no enabling disclosure for it to be -- there's no way that actually is possible based on Yang.

JUDGE PRATS: Well, actually, Yang says they turn off the luciferase gene. That seems to me that's evidence that, in fact, they did get overlapping and, in fact, it worked the same way as yours.

I understand the difference between the process that you're performing that uses manganese, and I understand what Gross says; but my concern is that you had the same enzyme, the same substrate, producing the same length molecules effective to, basically, represent sufficiently a number that will turn off luciferase genes.

So I'm not sure what's missing in Claim 13.

DR. STRIMPEL: Because what you said is, actually, factually incorrect. In reality you only need one fragment. One 20 to 23 or 22 or 21 nucleotide fragment to switch off a gene.

The problem is you don't always know which one you need. Sometimes you're lucky, sometimes you're not. The point of having a mixture of fragments which are representative of the whole means you need to know nothing about the thing at all.

Now, you can be lucky and, in fact, that's why instead of using enzyme mixes what is common and has been used is actually synthesizing fragments.

The problem is when you get this in Yang you get a lot of variability when they're trying to shut down one of the loops, I think it's R loop, they

get 900-fold reduction. When they shut down the other one, they get 400-fold.

They themselves say they get 50 percent, upwards of 50 percent of gene silencing. I feel doing experiments 50 percent gene silencing is not really good enough. It's not satisfactory.

That's why we want to have a substantial portion of the mixture so that you absolutely are likely to get the gene silencing that you seek, and that's actually what is proven that ours does, which is why Yang's Lab is using our mixture today and not theirs.

They're using RNaseIII in the presence of manganese in an unpublished cell paper because our mixture, with the manganese, results in a reliable outcome. It doesn't mean theirs won't work, it just means that they don't know whether they've got a sufficient number of fragments in order to effectively -- very effectively -- silence genes. They may be lucky, but they may not.

So the fact that they've got gene silencing per se doesn't mean the more silencing you've got the more fragments you've represented in the double-stranded RNA. It simply means you have an active fragment in the mixture.

JUDGE MILLS: Is there something in the interpretation of the blot in Figure 1B which would lead us to believe that we don't have a substantial portion to meet the claimed limitations?

DR. STRIMPEL: Yes.

JUDGE MILLS: Maybe it's the way -- is there other language in Yang? You said it was 500 -- I didn't quite follow that.

DR. STRIMPEL: The problem with Figure 1B is that you really don't know what you've got there except you've got some material that corresponds to the band which is marked, which is the control, which is the third column in 1B.

Without a proper size marker with multiple bands, you can't actually tell, and it's quite possible because it's ankylose gel that they have fragments in excess of 100 nucleotides there.

The fact is they've cut out a small band which corresponds to the 21 nucleotide. They then purify that on a second gel, and then they use that for gene silencing. So they've gone through a couple of different steps before they actually -- what you see in 1B is not the material they use for silencing. It's what they get from the gels in 1C.

JUDGE MILLS: But the ultimate material which they extracted from the gel and further purify, so to speak, might include a substantial portion of --

DR. STRIMPEL: The figure is very bad. We resorted to submitting as an attachment their paper, which is a little bit better. We actually have a poster which we've blown up of Yang's –

DR. TZERTZINIS: Do you want to put it up?

DR. STRIMPEL: Yeah, because that's a very important thing. You can see that most of the material is larger. So one would assume from that they were actually only recovering a small fraction of the total.

We actually delayed filing because -- the group decided it was actually extremely important to do this rather complicated experiment which they described in the application to demonstrate that you have got a reasonable

coverage of the double-stranded RNA. Otherwise, it wouldn't be a true random mixture.

JUDGE PRATS: He wants to post the --

JUDGE MILLS: The gel?

DR. STRIMPEL: We literally managed to use one of the papers just to highlight that figure a little bit.

JUDGE MILLS: This is the paper of record? Have you briefed this at all?

DR. STRIMPEL: Yes, this is -- yes, it was attached to the pleadings. It's exactly the same as what you've got in the patent, just slightly clearer. This is a band.

JUDGE MILLS: Do we have any product claim dependent on Claim 1? The method of Claim 1?

DR. STRIMPEL: No, we don't because Claim 1 is a method.

JUDGE MILLS: But we don't have a product made by the method in Claim 1?

DR. STRIMPEL: No.

JUDGE MILLS: Okay.

DR. STRIMPEL: We just have -- normally, you need to have -- these days you can't do that, I guess.

So Claim 1 is an important claim, which we haven't discussed and probably should spend a little bit of time on as well; but I think just to finish off on Claim 13, which is where the substantial portion comes in, your question is, you know, given that Yang uses magnesium and the fact they've

had to control -- just to get any material of the right size, they've had to control their digestion.

Then they have to purify a small portion of the sample and put it on another gel, and then use that for which they get silencing. Your question is how do you know that's not 20 percent?

Well, 20 percent is 1 in 5. You've got much larger pieces up here, significantly larger; but you don't know how large that is because there's no size marker. But the ankylose gel is -- you get quite a large range of sizes of ankylose gel.

So it's quite likely -- one of ordinary skill in the art, looking at this, would assume that they did not get 20 percent. I guess that's not a fact that we've proven conclusively, but it's certainly something that played out because people are using our methodology and they're not using magnesium. They're using manganese today. Even that lab that produced that data.

JUDGE PRATS: So, essentially, you're saying we don't have sufficient evidence to establish that the substantial represented limitation, whatever it is, is inherently present in Yang's digest, or at least the gel purified digest, correct?

DR. STRIMPEL: The experiments are very extensive to do that, and we think -- I didn't submit a declarations from scientists from another place to confirm what I'm saying, but –

JUDGE PRATS: Well, it seemed like during prosecution the Examiner tied Claim 13 to Claim 1.

DR. STRIMPEL: Yeah, which they're different. In Claim 1 the Examiner made a number of assumptions that were incorrect.

One of the key issues here is in order to use manganese you have to use higher concentrations of the RNaseIII. What she said is that's merely a way to get around the reference of Yang that we're using higher concentrations. It's clear from the figures in our application that this is not true. We tried a variety of concentrations and in Figure 1 we show exactly where it is desirable to get the results that we are claiming. It's absolutely quite clear in Figure 1D and in Figure 1C.

We do compare the ratio from micrograms of RNase3 to micrograms of substrate, and .2 is not good enough and .4 is fine. You get a nice clear band. At a ratio of .2 you get too much large double-stranded RNA. So it's not correct of her to say that we're simply coming up with this number which we wrote into the specification just to get around Yang. No, it's an extremely important limitation to Claim 1.

It's not suggested by Yang and certainly it's not suggested by Gross, who is trying to do something else and doesn't mention ratios.

So there are a number of assumptions the Examiner has made here in rejecting this which is simply factually wrong.

JUDGE MILLS: Is this table in the brief?

DR. STRIMPEL: Everything that's in the table is present in the brief. I prepared you a handout of this. I referenced every comment made. I'll hand it up, if you're willing to accept it.

It's all referred to in the references because the key argument -- there's so many small arguments that I felt it necessary to reduce it to this table to simplify where the issues were.

JUDGE MILLS: We're beginning to run short on time, so if you could summarize the table as quickly as you can.

DR. STRIMPEL: I'd like to say in the first case that Yang points out there's a problem with exhaustive digestion. This is not applicable in Gross. There's no discussion of exhaustive digestion or generating fragments of 12-15 base pairs as being a problem.

As a result of this problem, Yang played around with the amounts of enzymes he uses, which are .01:1 to .002, which is a hundred-fold less. Gross doesn't give a ratio and is not concerned with limiting digestion but rather studying the additional secondary cleavage that you can get with manganese over magnesium, which is an opposite effect to the one Yang would have wanted to use to limit his digestion.

He wasn't interested in enhancing his digestion and finding additional cleavage sites, which is what Gross described.

There no teaching in Yang about the portion of the sequence of a long double-strand -- this is related to Claim 13; and the gene silencing we discussed is also related to Claim 13.

So, basically, I just want to say why it doesn't help you to combine Yang with Gross. The basis of the brief that we presented is that Gross teaches away from Yang, but actually Gross is addressing a completely different problem and is not relevant at all to the problem at hand.

It would never be -- one of ordinary skill in the art would not go to Gross for a teaching in Yang; but even if they did, they would find that Gross taught away from Yang because Yang is trying to limit digestion and

Gross says, by the way, if you use manganese you get more cleavage, albeit specific cleavage, in the secondary site and provides an analysis of that.

So if there's a bottom line to this, how can you possibly use Gross to render our claim obvious in view of Yang because Gross has got nothing to do with either the problem nor would you turn to Gross for a solution for our problem separately. Because Gross is looking for additional cleavage by using manganese, not reducing the amount -- or preventing exhaustive digestion.

JUDGE MILLS: I believe we understand your position with respect to the case.

Just as a point of notation, it's not inappropriate to recite a product claim and then recite the method of making the product if you can ultimately distinguish the attributes of the product. For future reference.

DR. STRIMPEL: Yes, that's right. You have to distinguish a product, and the substantial portion was really the distinguishment.

JUDGE MILLS: Thank you.

(Whereupon, the proceeding at 10:12 a.m. was concluded.)